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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,693	01/29/2002	Andrew Shiau	19459-001001	9894

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,693	SHIAU ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,29-35,39-44,46,49-137,139-142,144-148,150,153 and 155* is/are pending in the application.

4a) Of the above claim(s) *1-25, 29-43, 49, 51-135, 140, and 141* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,46,50,136,137,139,142,144-148,150,153 and 155* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The applicant has been amended as requested in the communication filed February 16, 2006. Accordingly, claims 45, 47, 48, 138, 143, 149, 151, 152, and 154 have been canceled; claims 44, 136, 137, 139, 142, 150, and 153 have been amended; and new claim 155 has been entered.

Claims 44, 46, 50, 136, 137, 139, 142, 144-148, 150, 153, and 155 are under consideration.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. In particular, the application fails to comply with 37 CFR 1.821 (d), which states:

> "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

The non-compliance are found through out the specification, see for example the figure description, page 10, line 26, page 11, line 31, page 13, and page 19, in particular, example 1 at page 35 line 3 and 4; and claims 46, 48, 137, 138, 142, and 143. It should be noted that the results in appendixes 1 and 2 represents a disclosure of one or more polypeptide sequence. If the amino acid sequence representing the results in the appendixes is part of the sequence listing, the heading of the Tables should identify the polypeptide(s) by sequence identification number. If the sequence is not in the sequence listing, applicants must file a new paper copy of the sequence listing contain the sequences in the Tables, and a Computer Readable Form of the sequence listing (CRF) accompanied with a statement indicating that the paper copy of the sequence listing and CRF are identical and that they contain no new matter.

In response to the above, applicant has made a second effort to perfect his compliance with the sequence rule. Applicant, however, has failed to perfect his compliance with the sequence rules after entering the amendment filed 2/15/06. The amendment to the figure descriptions is inadequate because after stating the proteins names the amendment states "SEQ ID NO's: X-Y". The sequence identifier must follow the protein named immediately and should be referred to by only one sequence identifier. Applicants should note that SEQ ID NO: 27 differs from SEQ ID NO: 28 by insertion of Glu residue between Glu-139 and Phe 140, and deletion of residues 157-164. In addition, the amendment to the specification at page 37, line 4 render the entire paragraph confusing. SEQ ID NO: 27 and 28, which are presumably referring to hERα LBD, are 244 and 237 amino acid residues, respectively. The binding domain of hERα consists of residues 297-554 which is 258, and thus, it can't possibly be SEQ ID NO: 27 or 28. Also, a sequence identifier is required after DES-hERα LBD. All amino acid

residues describe the three dimension structure in the specification should be accompanied by a sequence identification number at each occurrence. Applicants are responsible for identifying all instances in the specification where compliance need to be perfected.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44, 46, 50, 136, 137, 139, 142, 144-148, 150, 153, and 155 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons set forth in the prior Office actions mailed 12/9/04 and 8/8/05.

In response to the above rejection, applicants argue that: (a) the specification replete with description of the identifying characteristics of each component (receptor, agonist, and activator) of the crystal, as well as the manner in which component bind to one another; (b) the 'correlation' desired by the examiner is not a requirement; and (c) the examiner has not given why the argument presented by applicants are not persuasive.

Applicants' arguments filed 2/16/06 have been fully considered, but they are found unpersuasive. Indeed, the specification is replete with descriptions of various components, which may be included in the claimed crystal, but the claims are not directed component of crystal. The claims are directed to a crystal comprising any of said components. Beyond the binary and ternary crystals described at page 37, the specification fails describe any other example of the binary or ternary complex in a crystal form. Thus, the claimed genus is represented by a single species, which is insufficient to describe the whole genus. While crystal composition is an important part of the crystal, crystals are described by their crystal forms, symmetry element present in the crystal, and the angles between the crystal axes known as α, β, and γ, see for example the crystals described in the specification at page 37. Second, the rejection presented in the first and second Office actions is based on the judgment of one of ordinary skill in the art whether applicants were in position of the full scope of the claimed invention or not at the time the application was filed. The ordinary skill in the art at the time of invention knew that obtaining a protein in a crystal for is highly unpredictable and highly dependent on many factors that include ionic strength, gravity, pH, precipitant used for crystallization, temperature, isoelectric point, the source of the

protein being crystallized, protein concentration, buffer, the identity of the salts in solution and their concentration, and the presence or absence of stabilize such as DTT. Thus, changing any of these factors including a single amino acid in the sequence would be expected to have a great impact on the crystallization of a protein and its complexes. Thus, he/she turns to the teaching of the specification to identify new teaching that support the position of the claimed invention such as description of many crystals and correlation between the composition of the crystal and crystallization conditions, and the teaching of the prior art. It appears that the applicants have difficulties under standing this rejection. In the previous Office actions, the examiner has not change his argument or restated his position in a different way. The rejection is always based on the failure of the specification to sufficiently describe the claimed invention in such a way that one of ordinary skill in the art would recognize applicants' position of the claimed invention. Also, the examiner was very clear in the previous Office action mailed 8/8/05 and stated how applicants may amend their claims to place the claims in condition for allowance. Finally, the examiner disagrees with the applicants' assertion that bringing a phase change of a material is within the capability of one of ordinary skill in the art. For example, transforming a protein or its complexes in solution to amorphous precipitate is within the ordinary skill in the art, but transforming a protein or its complexes to a crystal in specific space group and unite cell dimension is not. Claims 136, 137, 139, and 148 are yet another attempt for applicants to claim a broad unrestricted crystal forms which are not described in the specification.

New claim 155 is included in the above rejection because it is dependent on rejected claim 44. Applicants should note that the atomic coordinates describe a property (the structure) of the protein complex, whereas the X-ray diffraction pattern is a physical property of the crystal. The diffraction pattern is not disclosed in the specification.

Claims 44, 46, 50, 136, 137, 139, 142, 144-148, 150, 153, and 155 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the prior Office actions mailed 12/9/04 and 8/8/05.

In response to the above rejection, applicants assert that the subject matter to hand is not straightforward, and argue that the exact sequence crystallized 297-554 of the hERα is stated at page 37, lines 4-5. Also, applicants argue: claims 136, 137, 139, 148, and 153 are enabled and do not require any crystallization conditions.

Applicants' arguments filed 2/15/06 have been fully considered, but they are found unpersuasive. The examiner disagrees of the applicants' assessments of the degree of difficulties of the subject matter and the examiner choice of words. Example 1 of the specification describe the preparation of a protein consisting of Met-Asp-Pro tripeptide fused to the N-terminal of residues 297 through 554 of hERα, which produces a protein of 261 amino acid residues, possibly 260 amino acid if the N-terminal Met is

removed by the host cell. Applicants should note that the amino acid sequence of residues 297 through 554 is not disclosed in the specification and it should have been. The solvent accessible cysteines of the protein described above were carboxmethylated and presumably used to obtain the complex for crystallization, see the paragraph bridging pages 35 and 36. Example 1 further describe the preparation of the protein-ligand complex, see the paragraph bridging pages 35 and 36. In contrast, the specification at page 37, line 4, states that residues 297-554 crystallized. These contradictory statements in the specification are to say the least confusing by design, which is equivalent to evasive. To add to the confusion, applicants amended the paragraph beginning at lines 4 and of page 37 to insert SEQ ID NO: 27-30, and SEQ ID NO: 31. Nothing in the specification suggests that any of SEQ ID NO: 27, 28, and 31 was ever crystallized or their crystallization was attempted. While it is quit common that disorder portion(s) of an amino acid sequence are not observed or resolved in the three-dimensional structure of a protein, the crystallized protein containing those portions is well defined. It is what you put in the crystallization dishes, which the specification states that the complex was characterized by utrafilteration, SDS-PAGE, native PAGE, and electrospray ionization mass spectrometry, see page 36 lines 7 and 8. If the result of the electrospray ionization mass spectrometry experiment was included in the specification, we may have had a clue to the identity of the crystallized protein. It is what the ordinary skill in the art use to grow the crystal, and not what is observed in the structure.

The citation of Gilland *et al.* at page 46, last paragraph, of the response, is noted, but it is clear that applicants are miss reading the statement made at page 600, left column. Applicant miss the clause "crystallization is an empirical process", which means it is a hit or miss approach. In the same paragraph of Gilland *et al.* following the above statement, they state, "surprisingly, no generally accepted strategy has emerged, even though many suggestion have been put forth, with the exception perhaps of the implementation of fast screening procedure." With regard to applicants legal position articulated in March 9, 2005, the first Office action on the merit has sets out a *prima facie* case of non-enablement, explaining by sound scientific reasoning why a person of ordinary skill in the art would doubt that the guidance of the specification would enable practice of the full scope of the claimed invention without undue experimentation. Applicants have not provided sufficient evidence to rebut the *prima facie* case of lack of enablement. Finally with applicants alleging that the examiner has not addressed the dependent claims individually. None of the claims defines the specific protein, which produced the crystal of the invention, and the crystal itself as defined by the space group, unites cell dimensions, and the angles between the crystal axes. New claim 155 is dependent on claim 44 and does not cure its deficiencies.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 44-48, 50, 138, 142-147, 149, and 152 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for these rejections:

(a) The phrases "estrogen receptor α binding domain" in claims 44 renders the claim indefinite because the resulting claim does not define the metes and bound of the claimed invention. The "estrogen receptor α binding domain" remains indefinite because the claim does not define the boundaries of the claimed inventions. For examination purpose only, the phrase is assumed to be any fragment containing the ligand-binding site of an estrogen α binding protein, which makes the claim indefinite.

Applicants traverse the rejection and refer the examiner to page 36, of applicants' response of March 9, 2005.

Applicants' arguments filed 2/15/06 have been fully considered, but they are found unpersuasive. The examiner has provided adequate response to applicant arguments filed 3/9/05 in the previous Office action, mailed 8/8/05.

(b) The abbreviations or acronyms "GRIP1" in claims 136 and 139, and "o,p-DDT" in claims 136 and 139 are not defined at least once in the claims. It should be noted that the abbreviation "o,p-DDT" is not even defined in the specification at page 19, lines 23-25.

Applicants traverse the rejection and point out that the term is well known in the art and refers to "Glucocorticoid Receptor Interacting Protein 1".

Applicants' arguments filed 2/15/06 have been fully considered, but they are found unpersuasive. Although the phrase is deined in the specification, inserting the definition in the claim produces indefinite claim because of the phrase "(e.g. SEQ ID NO: 4)". With regard to the biphenyl compound which the examiner could not identify, and applicants would not tell us what is the name of the compound o,p-DDT. Applicants must present some evidence to show that the compound is known in the art by its abbreviation and not by its proper chemical name. Applicant should note that there is a biocidal compound used in massive scale in the 1940's and 1950's to kill insects with the abbreviation DDT. It is not a biphenyl compound.

(c) Claims 46, 50, 137, 142, 144-148, 150, 153, and 155 are included with these rejections because they are dependent on a rejected claim do not cure its deficiencies.

Allowable subject matter was noted in the previous Office action, mailed 8/8/05.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656